24/Appeal Brief (3)

PATENT
0933-0154P

Bet 10-30-02

IN THE U.S. PATENT AND TRADEMARK OFFICE

In re application of		Before the Board of Appeals	
Applicant:	Veli-Matti LEHTOLA et al.	Appeal No.:	
Appl. No.:	09/486,971	Group:	1615
Filed:	April 11, 2000	Examiner:	R. Bennett

For: PHARMACEUTICAL PREPARATION COMPRISING CLODRONATE AS ACTIVE INGREDIENT AND SILICIFIED MICROCRYSTALLINE CELLULOSE AS EXCIPIENT

BRIEF ON BEHALF OF APPELLANTS

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BRIEF ON BEHALF OF APPELLANTS

Honorable Commissioner for Patents
Washington, DC 20231

Pursuant to the Notice of Appeal filed August 16, 2002, the following Appeal Brief is respectfully submitted in connection with the above-identified application in response to the Examiner's final rejection of claims 1, 3, 4, 6, 11 and 14-19 dated April 16, 2002.

I. REAL PARTY IN INTEREST

The real party in interest of the present invention is Leiras Oy of Pansiontie 47 Turku, Finland FIN-20210, the assignee of the entire right and interest of the instant application. The assignment of said right and interest was recorded on September 25, 2000 at Reel 11110, Frames 0950-0952 to Leiras Oy.

II. RELATED APPEALS AND INTERFERENCES

There are no related appeals or interferences pending for the present application.

III. STATUS OF CLAIMS

Claims 1, 3, 4, 6, 11 and 14-19 are pending in the present application (see attached Appendix). Claims 1, 3, 4, 6, 11 and 14-19 were rejected under 35 U.S.C. § 103 (a), in the final Office Action of April 16, 2002. The rejection of claims 1, 3, 4, 6, 11 and 14-19 are hereby appealed.

IV. STATUS OF AMENDMENTS

No Amendments to the claims were made subsequent to the Examiner's final rejection of claims 1, 3, 4, 6, 11 and 14-19 on April 16, 2002. A Notice of Appeal was filed subsequently on August 16, 2002.

V. SUMMARY OF INVENTION

The present invention is directed to a tablet form of a pharmaceutical preparation for oral use that contains a pharmacologically acceptable salt of dichloromethylene biphosphonic acid, i.e., a clodronate, especially disodium clodronate, as its active ingredient and which contains silicified microcrystalline cellulose as an excipient (see page 1, lines 1 – 7 of the specification). The pharmaceutical preparation of the current invention may further comprise conventional gliding agents and lubricants, filling agents and/or disintegrants (see page 5, lines 7 – 27 of the specification). Because this pharmaceutical preparation comprises silicified microcrystalline cellulose (SMCC), it is possible to achieve oral dosage forms with acceptable size and uniform quality while also having a sufficiently high concentration of the active agent, clodronate, in the preparation (see page 3, lines 11-14 of the specification).

SMCC used in the pharmaceutical preparation of the present invention is comprised of microcrystalline cellulose which has been coprocessed with from about 0.1 to about 20% silicon dioxide based on the amount of microcrystalline cellulose. It is an agglomerate of microcrystalline cellulose and silicon dioxide in which the microcrystalline cellulose and silicon dioxide are in intimate association with each other. This means that the silicon dioxide has been integrated with the microcrystalline cellulose particles but there is no chemical interaction between the two materials. One means to achieve this is by spray-drying a suspension of microcrystalline cellulose and silicon

dioxide (see page 3, lines 20 – 28 of the specification). Using SMCC in clodronate preparations results in overall improved powder flow, compactibility, tablet strength and especially reduced friability (see page 3, lines 30-31 of the specification).

The present invention is also directed to a method for manufacturing said pharmaceutical preparation using SMCC. The pharmaceutical preparation of the present invention is manufactured by first mixing dry granules of clodronate with stearic acid, or stearic acid in an ethanol solution. The dried granules are then sieved and then mixed with croscarmellose sodium, SMCC, and magnesium stearate to form a mixture. Tablets are then formed with the resulting mixture using a tabletting apparatus. If desired, the prepared tablets can also be coated with a coating solution (see page 7, lines 4 – 14 and page 9, lines 1 – 2 of the specification).

VI. ISSUE TO BE CONSIDERED

Claim 1, 3-4, 6, 11, 14-19 stand rejected under 35 U.S.C. § 103 (a) as being unpatentable over Posti et al. (US Patent No. 5,525,354) in further view of Sherwood et al. (WO 96/21429) and Remington's Pharmaceutical Sciences. The Examiner alleges that "one of ordinary skill in the art would have been motivated to substitute 'silicified' microcrystalline cellulose for microcrystalline cellulose and silicon dioxide." (see page 2 of Advisory Action mailed July 30, 2002) The issue is whether the references, taken as a whole, suggest the claimed invention and whether there is any motivation to combine the references. Another issue is whether Appellants have demonstrated unexpected results.

VII. GROUPING OF CLAIMS

Appellants respectfully request that the claims be grouped as follows:

Group I – Claims 1, 4, and 6

Group II – Claim 3

Group III – Claims 11, 14, 17, 18 and 19

Group IV – Claim 15

Group V – Claim 16

VIII. ARGUMENTS

Group I

Claims 1, 4, and 6 recite a pharmaceutical preparation comprised of clodronate and SMCC. The Examiner has rejected these claims under 35 U.S.C. § 103 (a) over Posti et al. (Posti) in view of Sherwood et al. (Sherwood), in further view of Remington. The Examiner alleges that "one of ordinary skill in the art would have been motivated to substitute 'silicified' microcrystalline cellulose for microcrystalline cellulose and silicon dioxide." (see page 2 of Advisory Action mailed July 30, 2002) Appellants disagree with this allegation and assert that the Examiner has not successfully established *prima facie* obviousness. Appellants assert that the references, taken as a whole, do not suggest the claimed subject matter. Appellants further assert that there is no motivation to combine the teachings of Posti, Sherwood and Remington.

References Do Not Suggest Claimed Invention

> On pages 4-5 of the Office Action date April 16, 2002, the Examiner states that, "Remington discloses microcrystalline cellulose and silicon dioxide are known in the art as excipients for tableting, while Sherwood discloses the combination of the two has improved characteristics. Therefore, substituting one excipient, as taught by Sherwood, for two excipients as taught by Posti, would not only have the advantages taught by Sherwood, but would also add convenience to the overall process of making. The expected result would a tablet comprising dicholormethylene biphosphonic acid and microcrystalline cellulose-based excipient."

Appellants assert that Examiner's alleged expected result is insufficient and that one of ordinary skill in the art would deem the expected result to be a tablet, *that is enteric coated with a film that dissolves at a pH of 5 to 7.2,* comprising dicholormethylene biphosphonic acid and a microcrystalline cellulose-based excipient. This is not the same as the clodronate preparation of the present invention. The objective of the Posti reference is to "achieve a substantially improved bioavailability if the active agent is prevented from being transformed into its acid form, that is, if it is allowed to pass the stomach region in unliberated form into the lower digestive tract to be released at a site thereof which is optimal from the point of view of the absorption of the active

agent. According to the invention it has now been discovered that the said objective is reached if the preparation is a drug delivery form which is enteric coated with a film which dissolves at a pH of from 5 to 7.2." (see Posti, column 1, lines 31-42) It is readily apparent that the essential feature of the Posti invention is the enteric coating. The expected result of substituting the SMCC of Sherwood in the preparation in Posti, as proposed by the Examiner, does not suggest the clodronate preparation of the present invention – it is not obvious from the teachings of Sherwood and Posti, to prepare a clodronate preparation comprising SMCC that *does not require an enteric coating*. Even more notable is the fact that Posti does not provide some motivation or suggestion to prepare the clodronate tablet *without* the enteric coating. Since the references do not teach or suggest to make the claimed invention (see *In re Vaeck,* 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991)), obviousness has not been established and therefore Appellants respectfully request the honorable Board to reverse the Examiner with respect to the rejection of the claims of Group I under 35 U.S.C. § 103 (a).

No Motivation To Combine The References

In the Advisory Action dated July 30, 2002, the Examiner "refers to the Sherwood reference, wherein Sherwood discloses the advantages of 'silicified' microcrystalline cellulose to be superior compressibility and disintegrating properties. Therefore one of ordinary skill in the art would have been motivated to substitute 'silicified' microcrystalline cellulose for microcrystalline cellulose and silicon dioxide." Appellants disagree with the Examiner and maintain that there is no motivation to combine the Sherwood, Posti, and Remington references.

Sherwood states that it is an object of the invention to provide an excipient useful in direct compression and wet granulation methods which has improved compressibility (see Sherwood page 8, lines 13-20) and places particular emphasis on wet granulation (see Sherwood page 4, line 19 through page 5, line 27). Neither Posti, nor the present invention, however, utilize wet granulation or direct compression techniques to prepare their respective clodronate preparations as in Sherwood. Sherwood even states, "It is known that the exposure of the microcrystalline cellulose to moisture in the wet granulation process severely reduces the compressibility of this excipient." (Sherwood page 6, lines 1-5) It is therefore no surprise that Posti utilizes dry granulation rather than

wet granulation techniques in their preparation of the clodronate tablets using microcrystalline cellulose and silicon dioxide (not to be confused with SMCC). Furthermore, clodronate powder is so fine, voluminous, unflowing and sticky that neither direct compression nor wet granulation with any excipient can formulate the clodronate into acceptable tablets. Therefore, a case of obviousness has not been established due to lack of motivation to combine the teachings of Posti with Sherwood, even in view of Remington, because there is no motivation for Posti to modify its use of dry granulation techniques to switch to wet granulation as taught by Sherwood.

It should also be noted that Sherwood mentions that wet granulation is often used in connection with solid dosage forms wherein the amount of active ingredient is high compared to the amount of auxiliary agents. (see Sherwood page 4, lines 20-24) Appellants point out, however, that the examples of Sherwood describe the preparation of acetaminophen tablets which include only 30% by weight of active agent and 70% SMCC (see Sherwood, page 35, lines 9 to 11). In the present invention, the amount of clodronate is over 60% (64 to 68% in the examples) of the total weight of the composition, and wet granulation is not involved in the preparation of any ingredient of the clodronate tablet of the invention.

With regard to compressibility, Posti does not seek to solve the problem of improving the compressibility of its clodronate tablet – rather, it seeks to design a clodronate tablet with a drug delivery form that is enteric coated with a film that will dissolve at a pH of 5 to 7.2. Posti's primary desire is to improve where the clodronate is released in the digestive tract in order to achieve optimal absorption of the active agent (see Posti column 1, lines 31-42). With regard to disintegration, disintegration has not been a problem at any stage of the life-span of clodronate tablets, as clodronate is extremely water-soluble. Posti is concerned with the disintegration of the enteric coating at the proper pH, not the clodronate tablet itself. Therefore, there is no motivation to combine Posti and Sherwood since Posti does not provide any motivation to modify itself for the purpose of improving compressibility and disintegration in clodronate tablets.

In order to establish *prima facie* obviousness, the Examiner must meet three criteria: 1) there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to

modify the reference or to combine reference teachings; 2) there must be a reasonable expectation of success; and 3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must both be found in the prior art, no in applicant's disclosure. (see *In re Vaeck*, 947 F.2d 488, 20 USPQ2d 1438 (Fed. Cir. 1991))

The Examiner has not met this criteria, particularly because 1) the references do not suggest making a clodronate tablet comprising SMCC wherein the tablet does not have an enteric coating; 2) they do not disclose the decrease in friability of clodronate tablets when prepared with SMCC; and 3) there is no teaching or motivation to modify Posti to incorporate the teachings of Sherwood. Accordingly, Appellants respectfully request the honorable Board to reverse the Examiner with respect to the rejection of the claims of Group I under 35 U.S.C. § 103 (a).

Unexpected Results

It should also be noted that the friability of clodronate tablets of the present invention is low compared to the tablets as prepared in Posti which are far from the acceptable level with regard to industrial manufacturing standards and required quality of tablets in general (see the Declaration Under 37 C.F.R. § 1.132 submitted with Appellants' response filed March 22, 2002). Friability, meaning tablets are easily crumbled or split into pieces, is a problem particularly with tablets containing clodronate. This problem is overcome by using SMCC in the clodronate tablets, as in the present invention. One of ordinary skill in the art would expect, however, that the silicon dioxide in the SMCC would decrease crushing strength and increase friability, which is typical of such gliding agents. (see page 4, lines 10-16 of the specification) The March 22, 2002 Declaration clearly illustrates the favorable low friability characteristic of the present invention, however, none of the references cited by the Examiner disclose the benefit of low friability when preparing clodronate tablets comprising SMCC. Since the presence of a property not possessed by the prior art is evidence of nonobviousness (see *In re Papesch*, 315 F.2d 381, 137 USPQ 43 (CCPA 1963)) – in this case, that property being low friability - Appellants respectfully request the honorable Board to reverse the Examiner with respect to the rejection of the claims of Group I under 35 U.S.C. § 103 (a).

Group II

Claim 3 stands rejected under 35 U.S.C. § 103 (a) over Posti in view of Sherwood, in further view of Remington. All the arguments presented for Group I apply to Group II as well. Furthermore, Claim 3 provides further limitations to the pharmaceutical preparation of the present invention, particularly with regard to the percent by weight of anhydrous disodium clodronate and SMCC that comprise the present invention. Moreover, claim 3 indicates that a lubricant and/or disintegrant is also present in the tablet. The Examples in the specification as filed, as well as the experiments presented in the March 22, 2002 Declaration, illustrate that the present invention as claimed in Claim 3 results in clodronate tablets comprised with SMCC that are of superior quality, especially with regard to friability. Accordingly, Appellants respectfully request the honorable Board to reverse the Examiner with respect to the rejection of the claims of Group II under 35 U.S.C. § 103 (a).

Group III

Claims 11, 14, 17, 18 and 19 stand rejected under 35 U.S.C. § 103 (a) over Posti in view of Sherwood, in further view of Remington. All the arguments presented for Group I apply to Group III as well. These claims emphasize that SMCC is a key component of the present invention and recite a method by which SMCC is obtained. The purpose of these claims is to illustrate that SMCC is not simply a mixture of microcrystalline cellulose and silicon dioxide. As illustrated in the March 22, 2002 Declaration, clodronate tablets have more superior qualities, particularly with regard to friability, when prepared with SMCC rather than preparing them with separate amounts of microcrystalline cellulose and silicon dioxide.

Furthermore, it should also be noted that the tablets of the present invention can be prepared at higher tabletting speeds compared to tablets prepared with silicon dioxide and microcrystalline cellulose instead of SMCC. The tablets of the present invention can be prepared at higher tabletting speeds without having an advsere effect on the quality of the tablets. Example 8, beginning on page 10 line 25 of the specification, demonstrates that tablets NOT prepared with SMCC could not even be tabletted at a tabletting speed higher than 30,000 tablets/hour because the tablets would have broken up. Tablets that

can be prepared at a higher tabletting speed without adversely effecting the tablet quality, such as the tablets of the present invention, can have an increase in production rate thereby making the the production process a technically and economically favorable process (see the paragraph beginning on page 4 line 30 of the specification). Accordingly, Appellants respectfully request the honorable Board to reverse the Examiner with respect to the rejection of the claims of Group II under 35 U.S.C. § 103 (a).

Group IV

Claim 15, which is directed to a dry granulation manufacturing method, stands rejected under 35 U.S.C. § 103 (a) over Posti in view of Sherwood, in further view of Remington. All the arguments presented for Group III apply to Group IV as well. Claim 15 further indicates a method by which the present invention can be obtained. Appellants particularly want to emphasize that neither Posti nor the present invention utilize wet granulation or direct compression techniques to prepare their respective clodronate preparations as in Sherwood. Sherwood discloses that wet granulation is a preferred technique and is widely used (see Sherwood page 4, line 19 through page 5, line 27), however, the present invention is still successful in making high quality clodronate tablets despite not using wet granulation. Therefore, a *prima facie* case of obviousness has not been established due to lack of motivation to combine the teachings of Posti with Sherwood, even in view of Remington, because there is no motivation for Posti to modify its use of dry granulation techniques to switch to wet granulation as taught by Sherwood. Accordingly, Appellants respectfully request the honorable Board to reverse the Examiner with respect to the rejection of the claim of Group III under 35 U.S.C. § 103 (a).

Group V

Claim 16, which is also directed to a dry granulation manufacturing method, stands rejected under 35 U.S.C. § 103 (a) over Posti in view of Sherwood, in further view of Remington. All the arguments presented for Group IV apply to Group V as well. Claim 16 further indicates that the first mixing step is performed in an ethanol solution.

Using the ethanol solution does not make this a wet granulation method because the claim indicates that the granules are dried before sieving. Again, Appellants point out that neither Posti nor the present invention utilize wet granulation or direct compression techniques to prepare their respective clodronate preparations as in Sherwood. Sherwood discloses that wet granulation is a preferred technique and is widely used (see Sherwood page 4, line 19 through page 5, line 27), however, the present invention is still successful in making high quality clodronate tablets despite not using wet granulation. Therefore, a *prima facie* case of obviousness has not been established due to lack of motivation to combine the teachings of Posti with Sherwood, even in view of Remington, because there is no motivation for Posti to modify its use of dry granulation techniques to switch to wet granulation as taught by Sherwood. Accordingly, Appellants respectfully request the honorable Board to reverse the Examiner with respect to the rejection of the claim of Group IV under 35 U.S.C. § 103 (a).

CONCLUSION

The Honorable Board of Patent Appeals and Interferences is respectfully requested to reverse the rejection of the claims.

The required Appeal Brief fee under 37 C.F.R. § 1.17 (c) in the amount of $320.00 is attached hereto.

If the Examiner has any questions regarding the above matters, please contact Appellants' representative, Gerald M. Murphy, Jr. (Reg. No. 28,977), at the telephone number listed below.

If necessary, the Commissioner is hereby authorized in this, concurrent, and further replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fee required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

By _____
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GMM/CVC
0933-0154P

APPENDIX

CLAIMS UNDER APPEAL

Claim 1. (Amended) A tablet form of a pharmaceutical preparation comprising,

50 - 90% of a pharmacologically acceptable salt of dicholoromethylene biphosphonic acid as an active agent; and

5 - 25% of silicified microcrystalline cellulose.

Claim 3. (Amended) The preparation according to claim 1, comprising:

a) from about 60 to 80% by weight of anhydrous disodium clodronate;

b) from about 8 to 20% by weight of silicified microcrystalline cellulose; and

c) from about 0.5 to 10% by weight of lubricants and/or disintegrants.

Claim 4. (Amended) The preparation according to claim 1 or 3 wherein silicon dioxide is present in the silicified microcrystalline cellulose in an amount of from about 0.1 to 20% weight, based on the weight of the microcrystalline cellulose.

Claim 6. (Amended) The preparation according to claim 1 or 3, wherein the salt of dichloromethylene biphosphonic acid is the disodium salt.

Claim 11. (Amended) A pharmaceutical preparation, comprising,

a pharmaceutically acceptable salt of dicholoromethylene biphosphonic acid, and

an excipient, said excipient comprising silicified microcrystalline cellulose obtained by coprocessing microcrystalline cellulose with from about 0.1 to about 20% silicon dioxide, based on the amount of microcrystalline cellulose, to form an agglomerate of microcrystalline cellulose and silicon dioxide wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other and the silicon dioxide is integrated with the microcrystalline cellulose particles, but there is no chemical interaction between the two materials.

Claim 14. The process of claim 11 wherein the coprocessing is performed by spray-drying.

Claim 15. A method of manufacturing a pharmaceutical preparation according to claim 1, comprising:

mixing dry granules of a pharmacologically acceptable salt of dicholoromethylene biphosphonic acid with stearic acid;

sieving said granules;

mixing said granules with croscarmellose sodium, silicified microcrystalline cellulose and magnesium stearate to form a mixture;

forming tablets from said mixture in a tabletting apparatus; and optionally coating said tablets with a coating solution.

Claim 16. A method of manufacturing a pharmaceutical preparation according to claim 1, comprising:

mixing dry granules of a pharmacologically acceptable salt of dicholoromethylene biphosphonic acid with stearic acid in an ethanol solution;

drying and then sieving said granules;

mixing said granules with croscarmellose sodium, silicified microcrystalline cellulose and magnesium stearate to form a mixture;

forming tablets from said mixture in a tabletting apparatus; and optionally coating said tablets with a coating solution.

Claim 17. The process of claim 15 or 16 wherein the silicified microcrystalline cellulose is prepared by coprocessing microcrystalline cellulose with silicon dioxide wherein the microcrystalline cellulose and silicon dioxide are in intimate association with each other and the silicon dioxide is integrated with the microcrystalline cellulose particles, but there is no chemical interaction between the two materials.

Claim 18. The process of claim 17 wherein microcrystalline cellulose is coprocessed with from about 0.1 to about 20% silicon dioxide, based on the amount of microcrystalline cellulose.

Claim 19. The process of claim 17 wherein the coprocessing is performed by spray-drying.

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APPEAL BRIEF TRANSMITTAL FORM

Assistant Commissioner for Patents
Washington, D.C. 20231:

October 16, 2002

Sir:

Transmitted herewith is an Appeal Brief (in triplicate) on behalf of the Appellants in connection with the above-identified application.

☐ The enclosed document is being transmitted via the Certificate of Mailing provisions of 37 C.F.R. 1.8.

A Notice of Appeal was filed on August 16, 2002.

☐ Applicant claims small entity status in accordance with 37 C.F.R. § 1.27

The fee has been calculated as shown below:

☐ Extension of time fee pursuant to 37 C.F.R. §§ 1.17 and 1.136(a) -

☒ Fee for filing an Appeal Brief - $320.00 (large entity).

☒ Check(s) in the amount of $320.00 is(are) attached.

☐ Please charge Deposit Account No. 02-2448 in the amount of $0.00. A triplicate copy of this sheet is attached.

If necessary, the Commissioner is hereby authorized in this, concurrent, and future replies, to charge payment or credit any overpayment to Deposit Account No. 02-2448 for any additional fees required under 37 C.F.R. §§ 1.16 or 1.17; particularly, extension of time fees.

Respectfully submitted,

BIRCH, STEWART, KOLASCH & BIRCH, LLP

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